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Efficient Synthesis of a Variety of New Functionalized Oxacalixarenes by Ullmann Coupling Reactions

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We have developed an efficient method to synthesize a new type of oxacalix[4]arenes containing nitrogen functional groups in a single step, through *N*,*N*-dimethylglycine-promoted Ullmann coupling reactions starting from aryl dibromides in yields of up to 37 %. With a aryl difluoride as substrate, a large, fully aromatic crown ether **8** could be obtained in 25 % yield. Further functionalization of the nitrogen functional groups in the cores of these oxacalixarenes may offer new opportunities for constructing desirable molecular architectures and a range of nitrogen-based multidentate ligands.

Introduction

Calixarenes, [1*n*]metacyclophanes incorporating bridging carbon atoms, have attracted considerable research interest from supramolecular chemists for decades.[1] Surprisingly, heterocalixarenes are far less prevalent, although modulation of the calixarene skeleton by linking the aromatic rings with atoms other than carbon has the potential to impart new physical and chemical properties in this class of compounds. Very recently, investigations into sulfur-,[2] nitrogen-,[3] silicon-, and germanium[4]-bridged calixarenes have increased significantly because of the rapid development of synthetic methodologies, especially in the catalytic field. Oxygen-bridged calixarenes (named oxacalixarenes), however, are almost absent from the chemical literature. The formation of an oxacalix[4]arene was first reported in 1966[5] and was followed by several manuscripts from 1974 to 1976,[6] all of which utilized nucleophilic aromatic substitution (SNAr) to form the macrocycles. Only a few reports describing the synthesis of new oxacalixarenes have appeared over the past 29 years, however.[7,8]

In recent years much attention has been devoted to the synthesis and study of the properties of functionalized calixarenes, because of their potential utility as selective ionophores for various cations or anions, as supramolecular hosts for neutral guest molecules, and as non-viral DNA vectors.[9,10] Inspired by these versatile functionalized calixarenes incorporating bridging carbon atoms, here we wish to report facile methods to synthesize oxacalixarenes containing nitrogen functional groups, in which nitro groups can be converted into various other functional groups (e.g., amino groups). Further functionalization of the nitrogen groups in the new cyclophanes may offer new opportunities for constructing desirable molecular architectures. In addition, the presence of nitrogen functional groups at the core of a cyclophane is synthetically relevant for catalysis, since nitrogen serves as a versatile binding site for a variety of metal complexes.[11] Bidentate and tridentate nitrogen ligands, for example, are important for many catalytic transformations.[12]

Results and Discussion

We initially tried to synthesize the new functionalized oxacalixarenes through direct SNAr reactions between phenols and 1,3-difluoro-2-nitrobenzene or 3,5-dibromo-4-nitrotoluene as starting materials without any Cu catalyst, but all attempts failed, giving either very low yields or none of the desired product. We therefore chose the Ullmann reaction to construct those new functionalized oxacalixarenes bearing nitrogen functional groups in the cyclophane core. Ullmann ether formation reactions, in which aryl bromides or iodides react with phenols under basic conditions in the presence of copper salt catalysts, have been the focus of a number of recent studies because they provide very direct access to diaryl ethers.[13] They have traditionally been carried out under rather harsh conditions, usually at high temperature in pyridine as solvent. The yields are low to moderate, and reactions between electron-rich aryl halides and electron-deficient phenols typically do not work well. Classical Ullmann conditions are no longer state of the art, but

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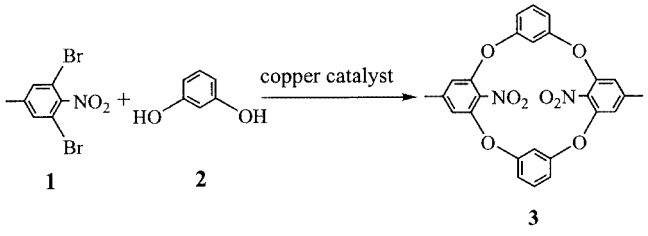
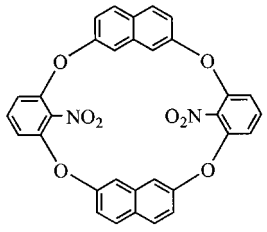
in recent years there has been great progress in Cu-catalyzed C–X bond formation under far less harsh conditions. Our initial investigations for the synthesis of the new oxacalix[4]-arene **3** involved a classic Ullmann ether reaction between 3,5-dibromo-4-nitrotoluene and resorcinol in the presence of simple copper salts without any extra ligand (Scheme 1). For this model reaction, we tried to optimize reaction conditions through the use of a variety of solvents (e.g., DMF, DMSO, pyridine, and *N*-methyl-2-pyrrolidine) (Table 1, Entries 1–4), bases (e.g., K_2CO_3, Na_2CO_3, $NaHCO_3$, KOH, NaH, and Cs_2CO_3), copper salts (e.g., CuO, CuI, CuCN, CuBr/dimethyl sulfide, and CuCl), concentrations, and temperatures (100–140 °C). We found that CuO/K_2CO_3/pyridine was the best choice of reaction system. Use of stoichiometric quantities of CuO could afford a 3% product yield at reflux for 1 day under highly dilute conditions (Table 1, Entry 1), whilst none of the desired product was observed via the direct SNAr reaction between resorcinol and 3,5-dibromo-4-nitrotoluene in the absence of CuO and ligand (Table 1, Entry 2). Unfortunately, all attempts to improve the yield of **3** failed.



Scheme 1. Synthesis of oxacalix[4]arene **3**.

Recent work with a copper(I) triflate catalyst in Buchwald's group has made it possible to carry out Ullmann ether reactions in good yields under milder conditions with a wider variety of substrates.[14] Unfortunately, use of this methodology still did not work well for the synthesis of the oxacalix[4]arene **3**, giving only a 4.5% yield (Table 1, Entry 5). Recently, a number of groups have reported using pyridine-type ligands, nitrogen-type ligands, 2,2,6,6-tetramethylheptane-3,5-dione (TMHD), or phosphane-type ligands in catalytic amounts to accelerate or enhance Ullmann reactions, allowing them to take place under more moderate conditions.[13,15] We were pleased to find that CuI/*N*,*N*-dimethylglycine was an efficient catalytic system for the Ullmann coupling reaction between 2,6-dibromo-4-nitrotoluene (**1**) and resorcinol (**2**) under highly dilute conditions, and the yield of oxacalix[4]arene **3** was improved dramatically. As summarized in Table 1, the results demonstrated that the choice of copper salts appeared to be highly critical for this reaction (Table 1, Entries 7, 10 –14). We also examined *N*-methylglycine and L-proline as additives for the reaction, but the yields were low due to poor conversion (Entries 8–9). The best result was obtained with Cs_2CO_3 as a base in the presence of a catalyst system generated in situ from *N*,*N*-dimethylglycine (40 mol%) and CuI (20 mol%) in dioxane at reflux, which gave a 37% yield (Table 1, Entry 7). It may be noted that our methodology also worked well for a coupling between 2,7-dihydroxynaphthalene (**4**) and 1,3-dibromo-2-nitrobenzene (**5**) to form the oxacalix[4]-arene **6** in a moderate yield (21%), whereas the classic Ullmann ether reaction in the absence of extra *N*,*N*-dimethylglycine gave only a 1% yield of **6**.



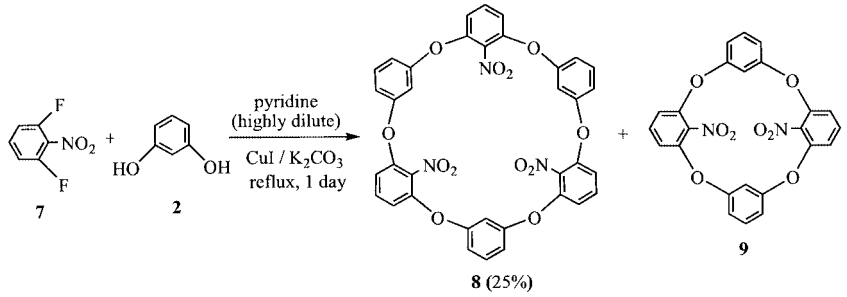
6

Large fully aromatic crown ethers are rare. The only two examples to have been reported, both in 1977, are hexabenzo-18-crown-6 and heptabenzo-21-crown-7, both obtained in low yields (<0.1%) by use of multiple Ullmann ether reactions.[16] Over the past 28 years only two manuscripts, by Gibb and co-workers in 2003 and 2001, describ-

Table 1. Ullmann coupling reactions between 3,5-dibromo-4-nitrotoluene (**1**) and resorcinol (**2**) to afford the oxacalix[4]arene **3** under highly dilute conditions.[a]

Run	Temp. [°C]	Base	Solvent	Copper salt[b,c]	Ligand	Yield [%][d]
1	100	K_2CO_3	pyridine	CuO	–	3
2	100	K_2CO_3	pyridine	–	–	none
3	140	K_2CO_3	DMF	CuO	–	1.5
4	140	K_2CO_3	*N*-methyl-2-pyrrolidine	CuO	–	1
5	100	K_2CO_3	pyridine	CuOTf	–	4.5
6	100	Cs_2CO_3	dioxane	CuI	–	none
7	100	Cs_2CO_3	dioxane	CuI	*N*,*N*-dimethylglycine	37
8	100	Cs_2CO_3	dioxane	CuI	*N*-methylglycine	4
9	100	Cs_2CO_3	dioxane	CuI	L-proline	5
10	100	K_2CO_3	dioxane	CuI	*N*,*N*-dimethylglycine	11
11	100	Cs_2CO_3	dioxane	CuOTf	*N*,*N*-dimethylglycine	15
12	100	Cs_2CO_3	dioxane	CuBr	*N*,*N*-dimethylglycine	18
13	100	Cs_2CO_3	dioxane	CuCl	*N*,*N*-dimethylglycine	18
14	100	Cs_2CO_3	dioxane	CuCN	*N*,*N*-dimethylglycine	7

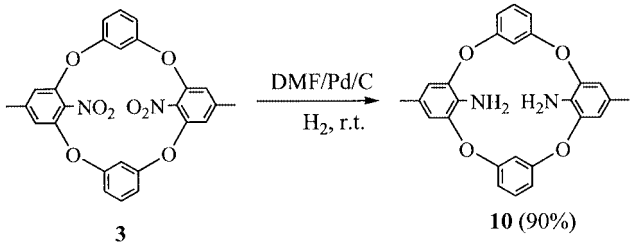
[a] Reaction conditions: 3.39 mmol of resorcinol, 3.39 mmol of 3,5-dibromo-4-nitrotoluene, copper salt, 0.4 mmol of extra ligand, and 6.78 mmol of base in 220 mL of solvent were heated at 100–140 °C under nitrogen for 1 day. [b] 1.0 equiv. of copper salt in the absence of extra ligand (Entries 1–6). [c] 0.2 mmol of copper salt in the presence of extra ligand (Entries 7–14). [d] Isolated yields.



Scheme 2. Synthesis of the large fully aromatic crown ether **8** under highly dilute conditions.

ing the synthesis of large macrocycles through Ullmann ether reactions with resorcinarenes as templates have appeared.[8c,8d] Our initial synthetic strategy to make the large oxacalix[6]arene **8** focused on the utilization of the CuI/*N*,*N*-dimethylglycine catalytic system, but this approach failed when we started from aryl dibromides (e.g., 1,3-dibromo-2-nitrobenzene or 3,5-dibromo-4-nitrotoluene). Very interestingly though, the fully aromatic crown ether **8** could be obtained by use of an aryl difluoride instead of an aryl dibromide. In the absence of *N*,*N*-dimethylglycine as additive, coupling between 1,3-difluoro-2-nitrobenzene (**7**) and resorcinol **2** promoted by the CuI/K_2CO_3/pyridine system afforded the [3 + 3] product **8**, in a 25% yield, rather than the [2 + 2] cyclophane **9** (Scheme 2), although the yield was not improved significantly when the extra ligand was employed. In addition, we did not observe any formation of large fully aromatic crown ethers with use of other dihydroxy aromatic derivatives (e.g., 2,7-dihydroxynaphthalene, hydroquinone, and 1,5-dihydroxynaphthalene).

In addition, we also tried to hydrogenate the NO_2 groups of aromatic crown ethers so that these oxacalixarenes might easily be further modified. We examined a range of solvents, such as $CHCl_3$, CH_2Cl_2, MeOH, MeOH/$CHCl_3$, and DMF, and found that DMF was the best choice. In the presence of 10% of Pd/C (5%), the oxacalix[4]arene **3** could be smoothly converted in a 90% yield into the aromatic crown ether **10**, containing amino groups (Scheme 3).



Scheme 3. Synthesis of the aromatic crown ether **10** with amino groups.

Conclusions

We have developed an efficient method to synthesize a new type of oxacalix[4]arene containing nitrogen functional groups in a single step through *N*,*N*-dimethylglycine-promoted Ullmann coupling reactions of aryl dibromides. We have also synthesize the fully aromatic crown ether **8** from the aryl difluoride. The nitro groups in the oxacalixarene could be smoothly converted into amino groups in high yield through hydrogenation. The diamine functionality can be readily functionalized for various nitrogen-based multidentate ligands that may potentially find applications in many metal-catalyzed transformations. Moreover, facile functionalization of the diamines into amides and peptide-based moieties offers opportunities to design new hosts for molecular recognition studies.

Experimental Section

General Ullmann Ether Reactions: A mixture of the dihydroxy aromatic derivative (resorcinol or 2,7-dihydroxynaphthalene, 3.39 mmol), the aryl dibromide (3,5-dibromo-4-nitrotoluene or 1,3-dibromo-2-nitrobenzene, 3.39 mmol), the copper salt (0.2 mmol or 1 equiv.), *N*,*N*-dimethylglycine (0.4 mmol), and Cs_2CO_3 (6.78 mmol) in 220 mL of solvent (dioxane or pyridine) was heated at 100–140 °C under nitrogen for 1 day. The solvent was concentrated under vacuum to give a brown solid, which could be purified by chromatography on silica gel with $CHCl_3$ as eluent to afford a white solid.

Oxacalix[4]arene 3: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.33 (s, 6 H), 5.28 (t, J = 2.4 Hz, 2 H), 6.85 (m, 8 H), 7.28 (t, J = 6.6 Hz, 2 H) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$, 25 °C): δ = 156.4, 150.2, 143.4, 127.9, 123.0, 110.3, 109.9, 106.1, 24.1 ppm. HRMS (FAB): calcd. for $[C_{26}H_{18}N_2O_8Na]$ ($[M + Na]^+$) 509.0961; found 509.0970. $C_{26}H_{18}N_2O_8$(486.1): C 64.20, H 3.73, N 5.76; found C 64.10, H 3.81, N 5.61.

Oxacalix[4]arene 6: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 6.51 (d, J = 2.5 Hz, 4 H), 7.26 (m, 8 H), 7.71 (d, J = 8.8 Hz, 2 H), 7.77 (d, J = 9.0 Hz, 4 H) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$, 25 °C): δ = 153.4, 149.9, 135.0, 134.2, 129.4, 126.4,124.1, 115.5, 114.8, 107.4 ppm. HRMS (FAB): calcd. for $[C_{32}H_{18}N_2O_8Na]$ ($[M + Na]^+$) 581.0961; found 581.0970. $C_{32}H_{18}N_2O_8$ (558.1): C 68.82, H 3.25, N 5.02; found C 68.70; H 3.40; N 4.93.

Synthesis of the Large Fully Aromatic Crown Ether 8: A mixture of resorcinol (3.14 mmol), 1,3-difluoro-2-nitrobenzene (3.14 mmol), CuI (6.28 mmol), and K_2CO_3 (6.28 mmol) in pyridine (250 mL) was heated at reflux for 1 day. The solid was filtered off and the filtrate was concentrated under vacuum to give a brown solid, which could be purified by chromatography on silica gel with $CHCl_3$/hexanes 8:2 as eluent to afford a white solid.

Oxacalix[6]arene 8: 0.18 g, 25%. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 6.51 (t, J = 2.0 Hz, 3 H), 6.67 (d, J = 8.5 Hz, 6 H), 7.06 (2 × d, J = 1.9, 2.0 Hz, 6 H), 7.30 (t, J = 8.6 Hz, 2 H), 7.44 (t, J =

8.8 Hz, 4 H) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$, 25 °C): δ = 156.3, 148.9, 134.0, 127.5, 125.8, 111.1, 109.8, 106.1 ppm. HRMS (FAB): calcd. for $[C_{36}H_{21}N_3O_{12}Na]$ ($[M + Na]^+$) 710.1023; found 710.1029. $C_{36}H_{21}N_3O_{12}$ (687.1): C 62.89, H 3.08, N 6.11; found C 62.77; H 3.19, N 6.03.

Supporting Information (see footnote on the first page of this article): General remarks, materials, other general synthetic procedures, and data including ^1H NMR, ^{13}C NMR, elemental analyses, and mass spectra are outlined.

Acknowledgments

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[1] a) C. D. Gutsche, *Calixarenes Revisited*, Royal Society of Chemistry, London, **2000** and references cited therein; b) V. Böhmer, *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 713–745 and references cited therein.
[2] a) H. Kumagai, M. Hasegawa, S. Miyanari, Y. Sugawa, Y. Sato, T. Hori, S. Ueda, H. Kamiyama, S. Miyano, *Tetrahedron Lett.* **1997**, *38*, 3971–3972; b) P. Lhoták, *Eur. J. Org. Chem.* **2004**, 1675–1692.
[3] a) A. Ito, Y. Ono, K. Tanaka, *New J. Chem.* **1998**, *22*, 779–782; b) A. Ito, Y. Ono, K. Tanaka, *J. Org. Chem.* **1999**, *64*, 8236–8241; c) Y. Miyazaki, T. Kanbara, T. Yamamoto, *Tetrahedron Lett.* **2002**, *43*, 7945–7948; d) M.-X. Wang, X.-H. Zhang, Q.-Y. Zheng, *Angew. Chem. Int. Ed.* **2004**, *43*, 838–842.
[4] B. König, M. H. Fonseca, *Eur. J. Inorg. Chem.* **2000**, 2303–2310 and references cited therein.
[5] N. Sommer, H. A. Staab, *Tetrahedron Lett.* **1966**, *7*, 2837–2841.
[6] a) F. P. A. Lehmann, *Tetrahedron* **1974**, *30*, 727–733; b) E. E. Gilbert, *J. Heterocycl. Chem.* **1974**, *11*, 899–904; c) F. Bottino, S. Foti, S. Papalardo, *Tetrahedron* **1976**, *32*, 2567–2570.
[7] Several groups have investigated the synthesis of compounds related to those in Refs.[5,6]: a) E. F. Boros, C. W. Andrews, A. O. Davis, *J. Org. Chem.* **1996**, *61*, 2553–2555; b) A. S. Abd-El-Aziz, C. R. de Denus, M. J. Zaworotko, C. V. K. Sharma, *Chem. Commun.* **1998**, 265–266.
[8] a) R. D. Chambers, P. R. Hoskin, A. R. Kenwright, A. Khalil, P. Richmond, G. Sandford, D. S. Yufit, J. A. K. Howard, *Org. Biomol. Chem.* **2003**, *1*, 2137–2147; b) R. D. Chambers, P. R. Hoskin, A. Khalil, P. Richmond, G. Sandford, D. S. Yufit, J. A. K. Howard, *J. Fluorine Chem.* **2002**, *116*, 19–22; c) X. Li, T. G. Upton, C. L. D. Gibb, B. C. Gibb, *J. Am. Chem. Soc.* **2003**, *125*, 650–651; d) C. L. D. Gibb, E. D. Stevens, B. C. Gibb, *J. Am. Chem. Soc.* **2001**, *123*, 5849–5850; e) J. L. Katz, M. B. Feldman, R. R. Conry, *Org. Lett.* **2005**, *7*, 91–94.
[9] C. D. Gutsche, *Calixarenes Revisited*, (Ed. J. F. Stoddart), *Monographs in Supramolecular Chemistry*, The Royal Society of Chemistry, Cambridge, U. K., **1998** and references cited therein.
[10] a) V. G. Organo, A. V. Leontiev, V. Sgarlata, H. V. R. Dias, D. M. Rudkevich, *Angew. Chem. Int. Ed.* **2005**, *44*, 3043 –3047; b) Y. Aoyama, T. Kanamori, T. Nakai, T. Sasaki, S. Horiuchi, S. Sando, T. Niidome, *J. Am. Chem. Soc.* **2003**, *125*, 3455–3457; c) R. Pinalli, V. Cristini, V. Sottili, S. Geremia, M. Campagnolo, A. Caneschi, E. Dalcanale, *J. Am. Chem. Soc.* **2004**, *126*, 6516–6517.
[11] A. Togni, L. M. Venanzi, *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 497–526.
[12] a) F. Fache, E. Schulz, M. L. Tommasino, M. Lemaire, *Chem. Rev.* **2000**, *100*, 2159; b) D. H. Camacho, E. V. Salo, Z. Guan, *Org. Lett.* **2004**, *6*, 865–868; c) D. H. Camacho, E. V. Salo, J. W. Ziller, Z. Guan, *Angew. Chem. Int. Ed.* **2004**, *43*, 1821–1825; d) C. T. L. Ma, M. J. MacLachlan, *Angew. Chem. Int. Ed.* **2005**, *44*, 4178 –4182.
[13] a) S. V. Ley, A. W. Thomas, *Angew. Chem. Int. Ed.* **2003**, *42*, 5400–5449; b) F. Theil, *Angew. Chem. Int. Ed.* **1999**, *38*, 2345–2347.
[14] J.-F. Marcoux, S. Doye, S. L. Buchwald, *J. Am. Chem. Soc.* **1997**, *119*, 10539–10540.
[15] a) E. Buck, Z. J. Song, D. Tschaen, P. G. Dormer, R. P. Volante, P. J. Reider, *Org. Lett.* **2002**, *4*, 1623–1626; b) C. Palomo, M. Oiarbide, R. López, E. G. Bengoa, *Chem. Commun.* **1998**, 2091–2092; c) D. Ma, Q. Cai, *Org. Lett.* **2003**, *5*, 3799–3802.
[16] D. E. Kime, J. Norymberski, *J. Chem. Soc., Perkin Trans. 1* **1977**, 1048–1052.

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